

Best Practice Criteria Agreement

PRINCIPLES OF GOOD RESEARCH PRACTICE IN BIOMEDICAL IMAGING

1	GOOD RESEARCH PRACTICE	2
2	STAGES OF GOOD RESEARCH PRACTICE.....	2
2.1	CONCEPTION / INITIALISATION	2
2.2	PLANNING STAGE.....	2
2.3	CONDUCTION OF EXPERIMENTAL WORK	4
2.4	EVALUATION	5
2.5	DISSEMINATION OF RESULTS.....	5
3	SPECIFIC GOOD PRACTICE METHODS AND ISSUES.....	5
3.1	TRAINING.....	5
3.2	ETHICAL ISSUES CONCERNING IMAGING IN CLINICAL TRIALS	5
3.3	GOOD CLINICAL PRACTICE.....	6
3.4	PRIVACY ISSUES.....	6
3.5	GOOD LABORATORY PRACTICE.....	7
3.6	TRIAL REGISTRATION	7
3.7	CONFLICT OF INTEREST.....	7
3.8	GOOD NOTEBOOK PRACTICE	7
3.9	ANIMAL EXPERIMENTATION REGULATIONS	8
4	CONCLUSIONS	8
4.1	EXPLORATORY RESEARCH	8
4.2	APPLICATION-DRIVEN RESEARCH.....	9
4.3	FINAL REMARKS	9
5	COMPILATION OF LITERATURE AND RELEVANT WEBSITES.....	10

1 Good Research Practice

The adherence of all researchers to principles of Good Research Practice is crucial to the scientific process. Such principles have been defined and formulated by various scientific bodies.¹ Good Research Practice is by definition not very specific, as the details will vary from field to field. The intended audience for EIBIR is broad enough as to diminish the usefulness of details.

Good Research Practice embodies a set of principles that provides a framework within which research is planned, performed, monitored, recorded, reported and archived. As the term "research" is very broad, Good Research Practice is a composite of several more specific Good Practice methods, plus additional general information:

The basic premises of good scientific practice are transparency and accountability. Good Research Practice is dependent on the integrity of researchers rather than the literal observation of a fixed set of rules. Integrity means honesty and openness in all aspects of the scientific work, in addition to adherence to basic ethical values in the work process. Given the increasingly strict limits on the length of articles, it is impossible to give every detail of one's methods in one's publications. Thus the reader – who is in fact the scientific community in general – must rely on the authors to have done their work correctly. Scientific work is not to be performed serendipitously but should follow an accountable process consisting of:

Conception / Initialisation

→ Planning

→ Conduction of Experimental Work

→ Evaluation

→ Dissemination of Results

Proper documentation should be made and archived for all stages of research. However, there is a fine line between good practice and needless bureaucracy. Investigators must strive for accountability, but not lose themselves in useless and resource-wasting administration. Plagiarism is to be avoided at all times.

2 Stages of Good Research Practice

2.1 Conception / Initialisation

- Thorough knowledge of the state-of-the-art, current questions in the field, and the priority of these questions.
- Use of international databases to find out state of the art.
- Imaging in clinical trials intends to improve the likelihood of early decision making: selection of patients and inclusion/exclusion criteria with clinical imaging, primary endpoint by modification in lesion over time with quantitative imaging.
- Need for a standardized design for imaging in clinical trials: designated clinical path for each well described pathology (clinical pathways).

2.2 Planning stage

- Clear statement of the research hypothesis.
- Definition of a research plan with consideration to the suitability, legality, and ethical standard of the methods to be used and to the relevance of goals to be achieved.

¹ In 1995, the Committee on Standards in Public Life ("Nolan Committee") identified seven principles of public life: selflessness, integrity, objectivity, accountability, openness, honesty and leadership. (see <http://www.mrc.ac.uk/PolicyGuidance/EthicsAndGovernance/GoodResearchPractice/index.htm>)

Further and more detailed information on Good Research Practice can be obtained from the national science agencies of the member states or via the web (in English), e.g. on the homepages of the Medical Research Council, the Research Services Division of the University of Cambridge, and the Wellcome Trust.

- Definition of a clear and transparent experiment protocol based on the research plan, in which the details of the methods to be used for data acquisition, analysis, and (internal) reporting are documented as well as the parameters and endpoints.
 - o Imaging to observe biomarkers may be more efficient than clinical endpoints (e.g. overall survival, symptom endpoint, complete response, time to progression).
 - o Statistically significant change in an image over time can demonstrate efficacy.
 - o If possible, use internationally accepted, standardized scoring and reporting systems such as the RECIST criteria or the CONSORT guidelines.

Reporting Guidelines²

Initiative	Title of study	Type of study	Source
CONSORT	Consolidated Standards of Reporting Trials	randomised controlled trials	http://www.consort-statement.org
STARD	STAndards for the Reporting of Diagnostic accuracy studies	studies of diagnostic accuracy	http://www.stard-statement.org
QUOROM	Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement	systematic reviews and meta-analyses	http://www.consort-statement.org/mod_product/uploads/QUOROM%20Statement%201999.pdf
STROBE	STrengthening the Reporting of OBServational studies in Epidemiology	observational studies in epidemiology	http://www.strobe-statement.org
MOOSE	Meta-analysis Of Observational Studies in Epidemiology	meta-analyses of observational studies in epidemiology	http://www.consort-statement.org/mod_product/uploads/MOOSE%20Statement%202000.pdf

- Consult with statistician to determine suitable endpoints and to create a statistical road-map for the study.
- Create reliable transparent reporting forms (such as a CRF in clinical trials).
- Creation of transparent distribution and archiving systems for data and protocols.
 - o Requirements for electronic data distribution and storage: security, compatibility, performance, simplicity, automatic back-up
- Creation of procedures for standardization and quality control
- Define image processing, manipulation and analysis tools to be used, PACS (Picture Archiving and Communications System)/reading station
- Create procedures for dealing with incidental findings, if applicable³.
- Registration of research plan into international databases, especially clinical trial registration (ICMJE homepage).
- Contact with sponsor/CRA/granting organisation:
 - o Legal documents should protect freedom of publication, also if results are not in the company's best interests.
 - o Legal documents should guarantee academic publication prior to any other publication or press release.

² Following ICMJE, "Uniform Requirements for Manuscripts Submitted to Biomedical Journals", Section IV.A.1.b. Reporting Guidelines for Specific Study Designs

³ Federa CHR, ER, CHT

- The question of ownership of intellectual property (the researcher – the research unit – the financier?) should be cleared in advance. The industry as financing partner should receive limited licensing rights, depending on the extent of support.
 - Determine what will be needed to justify expenditures/fulfil requirements, and plan accordingly.
- Perhaps the most difficult task, finding the fine line between too much bureaucracy and necessary and useful documentation.
- Practical organization of a clinical trial:
 - Internal contacts and organization: feedback medical administration, referring departments, investigator, and financial department.
 - Review safety issues, especially radiation exposure.
 - Supervisory responsibility should be made clear and documented.
 - Introduction of the protocol, qualified technology, qualified operators, ensure compliance with image acquisition/reconstruction protocol.
 - Training of qualified readers.
 - Image processing and transmission.
 - Image quality control testing: phantoms/time points.
 - Reference information database to evaluate response (<http://qforge.nci.nih.gov/projects/rider/>); American college of radiology imaging network (<http://www.acrin.org/>).
- Special Case: Evaluating Computer-Aided Detection (CAD)
 - The issue of evaluating the performance of Computer-Aided Detection (CAD) algorithms is becoming a critical one, as these systems are becoming widely used as decision support tools. It is therefore becoming very important to issue recommendations for retrospective and/or prospective study designs, in addition to the Burhenne study design⁴ that has been used in the past to evaluate Computer-Aided Detection accuracy. This topic is presently being evaluated by the FDA (USA).
 - The appropriate controls for reader studies, specifically whether studies should include unaided double reading by one or two readers, or reading aided with a sham CAD, in which the sham CAD randomly places the same number of marks on an image as the CAD algorithm being evaluated.
 - The appropriateness of using standardised weighted analysis as a primary or secondary analysis of a CAD study; weighted analysis would potentially minimise the distribution of clinical variables that make it difficult to compare multiple studies of a CAD algorithm's performance.
 - Whether different summaries of per-patient results should be considered to assess the robustness of per-patient conclusions as a unit of analysis; other unit types that are evaluated include per-region and per-lesion analysis.

2.3 Conduction of Experimental Work

- Observation of ethical rules and guidelines for experiments on humans and animals. The well-being of the human or animal subject should be seriously considered, not only in the planning, but also in the day-to-day execution of a study.
- Observation of all legal and regulatory requirements pertinent to the experiments.
- Adherence to the experimental protocol and detailed documentation of any amendments to or adaptations of this protocol as well as the reasons for these changes.
- Detailed documentation of the data acquisition process and of the data acquired, including who has performed what portions of the experimental protocol.
- Proper use of all equipment.

⁴ Burhenne, "Potential Contribution of Computer-aided Detection to the Sensitivity of Screening Mammography"

- Real time results and simultaneous transmission to different core labs/reviewers
- Technology and interaction between imaging site, imaging core lab, reader and sponsor.
- Attention to reporting criteria: what documentation is needed for justification of expenses/fulfilment of requirements.

2.4 Evaluation

- All data acquired should be taken into consideration in the evaluation and work-up of experiments. Data should be excluded only for acceptable and well-documented reasons (experimental failures, defects in the measurement), not because results do not adhere to the researcher's expectations.
- Adherence to the analysis procedures given in the experimental protocol and detailed documentation of any amendments to or adaptations of these procedures as well as the reasons for these changes.
- Detailed documentation of the data analysis process and of the results obtained, including who has performed what portions of the analysis procedure.
- Use of well-defined, documented and verified procedures, algorithms and software for data evaluation.
- Adaptation of the hypothesis on-the-fly, and especially reformulating it to a more suitable hypothesis based on the experimental results, is forbidden.

2.5 Dissemination of Results

- Dissemination is not an add-on, but an integral part of research: A result is only a result once it has been published. Not publishing publicly funded research is a misuse of taxpayers' money. Scientifically, refutation of a hypothesis is as valid an outcome as confirmation, and it should also be published.
- Coverage and acknowledgement of any pertinent previous work in the dissemination through publications, presentations etc.
- Description of results which neither overemphasises positive findings nor hides possible pitfalls and failures.
- Acknowledgement of contributions of all scientists involved (see ICMJE Requirements for Authorship).
- Once results have been published, all experimental details and data should be available to fellow scientists.
- Any real and potential conflict-of-interest needs to be declared.
- Research must be published in a journal before the industry publishes press releases; this should be included in any commercial contract.
- Follow internationally accepted reporting guidelines.

3 Specific Good Practice Methods and Issues

3.1 Training

Research leaders are responsible for providing leadership and guidance to upcoming scientists. Not only is appropriate training of science and scientific skills necessary, but also pertinent skills such as project management, writing of publications and grants, and teamwork should be in the training package of young researchers.

3.2 Ethical Issues Concerning Imaging in Clinical Trials

Patient information and 'reasonable' compensation, related to time, effort and inconvenience: a potential trial patient must be able to relate on a personal level (as goes for healthy volunteers).

Review radiation exposure and minimize number of images to be taken

<http://www.neirb.com> Institutional Review Board for subject recruitment: ethical review.

3.3 Good Clinical Practice

Good Clinical Practice gives guidelines for performing clinical trials, including ethical aspects, notation and archiving.

- <http://www.fda.gov>: critical is a good clinical practice in clinical trials; Imaging Guidance and safety assessments; Center for Devices and Radiological Health
- European Counterpart: EMEA, <http://www.emea.europa.eu>, Good clinical practice: <http://www.emea.europa.eu/Inspections/GCPgeneral.html>
- Clinical trial directive and good clinical practice directive EC: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol1_en.htm
- "... [T]he MRC has published separately *MRC Guidelines for Good Clinical Practice in Clinical Trials*, to which researchers should refer."⁵

"In clinical studies, the rights, safety, and wellbeing of participants must be safeguarded."⁶ All members of the staff must be informed and trained to work according to these guidelines.

3.4 Privacy Issues

"[Human subjects] have a right to privacy [that should not be infringed without informed consent. Identifying information, including [subjects'] names, initials, or hospital numbers, should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the [subject] (or parent or guardian) gives written informed consent for publication. Informed consent for this purpose requires that a [subject] who is identifiable be shown the manuscript to be published. Authors should disclose to these [subjects] whether any potential identifiable material might be available via the Internet as well as in print after publication. ... Identifying details should be omitted if they are not essential."⁷

Different kinds of data can be discriminated: anonymous data, directly-identifying personal data, indirectly-identifying personal data, and encoded data. Investigators should anonymize or encode data before data processing and analysis if at all possible. Anonymization is to be preferred unless future coupling of data to personal information may be necessary (e.g. in the case of incidental findings or if data is being collected prospectively), in which case data should be encoded for research use. Document and limit what third party holds the key to the encoding; it should not be available to the researchers.

Investigators should also be aware that not all encoding systems assure anonymity:

"As a datum acquires more specific characteristics, it comes closer – either in combination with other data or not – to becoming an identifying datum. The profession "Minister President" is without a doubt identifying. The occupation "violin maker" becomes identifying when combined with the first two numbers of the postal code."⁸

The following list gives the preference order for the format in which data should be used, as regards privacy issues. Uppermost is the most unidentifiable type of data, and the data becomes more identifiable as the list descends.

- anonymous and not coded,
- anonymous and coded,
- indirectly identifying and not coded,
- indirectly identifying and coded,
- directly identifying⁹.

⁵ Medical Research Council, "MRC Guidelines for Good Clinical Practice in Clinical Trials"

⁶ MRS, "Good Research Practice", p. 3.

⁷ ICMJE, "Uniform Requirements for Manuscripts Submitted to Biomedical Journals", Section II.E.1. Patients and Study Participants

⁸ Federa CHR, page 2-3, and Federa ER, page 6 and 7

⁹ Federa ER, page 12

3.5 Good Laboratory Practice

Good Laboratory Practice gives guidelines for performing laboratory experiments, including e.g. development of RF coils, MRI sequences, testing probes, animal experiments, but NOT clinical trials. Good Laboratory Practice does not cover ethical aspects (e.g. of animal use).

"For near-market projects sponsored by industry and some other funders, the more rigorous requirements of Good Laboratory Practice may be mandatory. [¹⁰]" Industry-sponsored research for the use of regulatory agencies (e.g. FDA) should be governed by these stronger regulations.

3.6 Trial Registration

Registering trials prevents repetition of trials, especially those that do not show effect, but is ripe for misuse by groups with higher patient flow. This should be made in accordance to the recommendations of the WHO; see the WHO International Clinical Trials Registry Platform ¹¹. For WHO purposes, the database MUST fulfill certain criteria. There are only a few databases that qualify, of which these are the most widely accessible.

Possible international databases are, e.g.,

- <http://www.isrctn.org/> (International Standard Randomised Controlled Trial Number, owned by Current Controlled Trials)
- <http://clinicaltrials.gov/> (produced by the National Library of Medicine)

3.7 Conflict of interest

To judge whether one is in a situation of conflict of interest, one should pay attention to how situations can be perceived by others.

"Conflict of interest exists when an author (or the author's institution), reviewer, or editor has financial or personal relationships that inappropriately influence (bias) his or her actions (such relationships are also known as dual commitments, competing interests, or competing loyalties). These relationships vary from those with negligible potential to those with great potential to influence judgment, and not all relationships represent true conflict of interest."¹²

"Researchers should automatically ask themselves "Would I feel comfortable if others learnt about my secondary interest in this matter or perceived that I had one?" If the answer is no, the interest must be disclosed and addressed appropriately."¹³

3.8 Good Notebook Practice

Good Notebook Practice gives guidelines for notation and archiving of (laboratory) data.

"A laboratory notebook is a complete legal document recording your work in the laboratory. Laboratory notebooks are vital in proving that you conducted the research. A properly kept laboratory notebook is invaluable in proving the right to own a related patent in Australia, or obtain one in the United States (where patent rights are assigned on a 'first to invent' basis, rather than the 'first to file' system that applies in Australia). One of the most effective methods to prove you were the 'first to invent' something is via a well-kept laboratory notebook. This short guide is designed to help you practice good laboratory notebook practices.

Electronic laboratory notebooks are becoming more widely used, but electronic records are not currently as effective as evidence of invention. At present, paper-based records are preferred as they cannot be easily altered; this is likely to change in the future however. Any electronic records should be printed out and affixed in your laboratory notebook."¹⁴

A laboratory notebook should therefore be kept up-to-date, with consecutively numbered pages and dated, hand-written entries signed by the author and, ideally, a witness.

¹⁰ OPSI, "The Good Laboratory Practice Regulations 1999"

¹¹ WHO International Clinical Trials Registry Platform <http://www.who.int/ictrp/en/>

¹² ICMJE, "Uniform Requirements for Manuscripts Submitted to Biomedical Journals", Section II.D. Conflicts of Interest

¹³ MRS, "Good Research Practice", p. 4.

¹⁴ IP Australia, "Practise Good Lab Book Practices"

- R** - **Record ALL laboratory information** in a bound notebook ... using indelible ink. Use each page of the notebook. If blank spaces must be left, draw a line diagonally through the blank space, and sign and date. Record everything. State your hypothesis, materials and methods, data and conclusions. ...
- E** - **Each entry** must be signed and dated by the person doing the work. ...
- C** - **Corroborate all entries** by an additional, knowledgeable party (e.g., the Principal Investigator) who reads, co-signs, and dates all entries.
- O** - **Original entries** should never be erased. If a mistake is made, draw a single or double line through the mistake and sign and date the correction in ink.
- R** - **Review and retain all records.** Records should be safely retained as long as necessary. ...
- D** - **Data generated or stored** on a computer must be printed out, permanently bound, signed and dated, and corroborated.¹⁵

3.9 Animal experimentation regulations

Animal experimentation must comply with national and international regulations, and all animals should be treated humanely according to Institutional Animal Care and Use Committee guidelines.

The 3R Principle should be implemented whenever possible:

Replace: Wherever possible, animal studies should be replaced by experiments ex vivo.

Reduce: Where animal studies cannot be avoided, use experimental designs which maximize the amount of information per animal or reduce the total number of animals needed to obtain the same information. Always use a few animals as possible; however, one should always use sufficient numbers of animals to achieve statistically significant data. All animal experiments should be controlled by a supervisory board to avoid potential overlaps and unnecessary duplication of animal experiments.

Refine: Develop and use alternative methods which allow equivalent data to be collected with less use of animals or less pain and stress for the animals used.

As an example, MR imaging allows repetitive and safe measurement of animals over long time periods, **reducing** animal use. Use of MRI to acquire data may also be considered **refinement**, as it is less invasive than alternative methods of data acquisition.

4 Conclusions

Details of implementation of Good Research Practice depend on the type of work to be performed:

4.1 Exploratory Research

Exploratory research is performed at the initialisation and innovation stage of some new scientific principle, concept, idea or method. Exploratory research is dedicated to explore the potential relevance, usefulness and practical application of a scientific innovation. It should be performed with an open mind to allow full exploration of the potential for a broad range of pertinent fields. Premature fixation to some specific application may leave the full potential to other fields undetected and unexplored. Research plans should be flexible; nevertheless structure and documentation of the research remain paramount. The scientist should formulate a tentative hypothesis and a plan for testing this hypothesis, should test the hypothesis, documenting any changes in the plans, and should discard/adapt the hypothesis based on proven and documented analysis methods. Exploratory research should not be performed for the sake of itself, but should always follow clear and relevant but flexible goals.

¹⁵ Technology Transfer, "TT Tip: Record Keeping/Laboratory Notebooks"

4.2 Application-Driven Research

Application-driven research is performed once a field has developed to the stage at which a clear hypothesis can be formed and tested with well-established methods. The direction and hypothesis of such research should be developed to pursue objectives and goals of relevance for the field. The research plan needs to be formulated with utmost care and scrutiny, as scientists must adhere to the working hypothesis until the study is completed.

In practice research projects may contain elements of both types of research. In this case, the scientist can and should still apply the principles of Good Research Practice. Defining suitably sized steps within the research plan and adapting the frequency/density of milestones will give opportunity appropriate decision making and for redefinition of direction at suitable intervals.

Whatever the type of research, the research path must be fully transparent and documented. While retrospective redefinition of goals to fit to the results is not admissible, a new and unexpected finding may be reported as such, but it will need to be confirmed by follow-up experiments using a proper hypothesis and research plan.

4.3 Final Remarks

Participation in the scientific process should be exclusively dependent on expertise, knowledge and skills, neither on hierarchical considerations nor on membership in a specific constituency or interest group. Institutions should endeavour to create an open and interdisciplinary research climate, encouraging researchers to develop their skills and to discuss their ideas.

In closing, Good Research Practice is an ideal towards which all researchers, no matter their field or type of research, should strive. The basic premises of transparency and accountability, together with the integrity of researchers both individually and as a whole, provide a structure which allows high quality research to flourish while making best use of available funds.

5 Compilation of Literature and Relevant Websites

- Abraham, Jerrold L., Charu Thakral, "Tissue distribution and kinetics of gadolinium and nephrogenic systemic fibrosis", *European Journal of Radiology*, May 2008, pp. 200-207
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- ACRIN: American College of Radiology Imaging Network; <http://www.acrin.org>
- Bellin, Marie-France, Aart J. Van Der Molen, "Extracellular gadolinium-based contrast media: An overview", *European Journal of Radiology*, May 2008, pp. 160-167
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- Bongartz, Georg, Michael Mayr, Deniz Bilecen, "Magnetic resonance angiography (MRA) in renally impaired patients: When and how", *European Journal of Radiology*, May 2008, pp. 213-219
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- DiMI: Diagnostic Molecular Imaging (European Network of Excellence); <http://www.dimi-net.org>
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use,
http://europa.eu/eur-lex/pri/en/oj/dat/2001/l_121/l_12120010501en00340044.pdf
- Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances,
<http://europa.eu.int/eur-lex/lex/LexUriServ/LexUriServ.do?uri=OJ:L:2004:050:0044:0059:EN:PDF>

- Directive 2004/9/EC of the European Parliament and of the Council of 11 February 2004 on the inspection and verification of good laboratory practice (GLP),
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- EANM: European Association of Nuclear Medicine; <http://www.eanm.org>
- EFGCP: European Forum for Good Clinical Practice; <http://www.efgcp.be/>
- EMIL: European Molecular Imaging Laboratories (European Centre of Excellence);
<http://www.emilnet.org>
- ESMI: The European Society of Molecular Imaging; <http://www.e-smi.eu>
- ESTRO: The European Society for Therapeutic Radiology and Oncology; <http://www.estro.be>
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- Federa CHT – Code for adequate secondary use of tissue (2001), consisting of the document Code of Conduct: "Proper Secondary Use of Human Tissue", homepage of the Dutch Federation of Biomedical Scientific Societies
<http://www.federa.org/?s=1&m=99>, Section "Self-regulatory codes of conduct"
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